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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/351,778	07/12/1999	WILLIAM S. M. WOLD	16153-7775	1203

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EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/351,778	WOLD ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-9,11-44,60-84 and 97-108* is/are pending in the application.

4a) Of the above claim(s) *6-9,16-19,23,25-31 and 76-84* is/are withdrawn from consideration.

5)☒ Claim(s) *5* is/are allowed.

6)☒ Claim(s) *11-15, 20-22, 24, 32-44, 60-75, and 97-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Claims 6-9, 16-19, 23, 25-31, and 76-84 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

Specification

The disclosure is objected to because of the following informalities: The descriptions of Figure 6 (page 8) and Figure 10 (page 9) refers to Figures 6A-6D and Figures 10A-10C, respectively. The panels of Figures 6 and 10 of the formal drawings filed 8/1/00 are not labeled A, B, C, etc.

Appropriate correction is required.

Claim Objections

Applicant remains advised that should claim 15 be found allowable, claim 63 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other

as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Although the independent and dependent claims from which each depends differ in scope with respect to the adenovirus vector, claims 15 and 63 do not. The method steps recited in claims 13 and 14 are the same as recited in claims 60 and 62, although worded differently. Thus the scope of claims 15 and 63 appear to be the same.

Claim Rejections - 35 USC § 112

Claims 11-15, 20-22, 24, 32-44, 60-75, and 97-108 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13, 60, 101, 102, and claims dependent therefrom recite "method for treating cancer in an animal having a tumor." Applicant has not indicated where support for this limitation, in particular recitation of "animal," is supported by the original specification. It is Applicant's burden to indicate where such support may be found. See MPEP 714.02, last sentence of the third paragraph from the end and 2163.06 (I) last sentence. Animals include organisms from protozoans to sponges and on up to mammals. It is unclear that simple animals even develop anything one would call cancer. Page 1, line 10 states that the vectors of the invention are for treating human cancer, and the specification refers to treating cancer in "patients," which when read in light of page 1, line 10, would be human patients. It is unclear

that the original specification teaches using the method to treat cancer in mammals generically, much less extending to other animals as recited.

With respect to claim 13 and its dependent claims, claim 13 has been amended to include the limitation that overexpression of ADP is defined by overexpression of ADP by the adenovirus vector relative to dl309. Applicant indicates the new limitation is supported by page 5, lines 18-22; page 12, lines 18-21, and Example 1. However, dl309 is not wild type, and there is no evidence that dl309 expresses ADP as high as any previously known adenovirus, nor was expression of ADP in dl309 or KD and GZ vectors measured as molecules of ADP per viral genome, as per page 12, lines 18-21. With respect to Example 1 of the specification, these portions of the original specification describe characterization of the disclosed KD and GZ vectors, and comparison of ADP expression of A549 cells transfected with each these vectors or with dl309, *dl*01/07, and dl327 *inter alia*. KD vectors are compared to dl309 as well as to *dl*01/07, and GZ vectors are compared to *dl*01/07 as well as to dl309 at 24 hour post-infection. However, at 36 hour post-infection KD vectors are compared only to *dl*01/07 and GZ are compared only to *dl*309. This description only refers to the KD and GZ vectors, and does not describe such a comparison as being generally determinative of an adenovirus vector overexpressing ADP. There is no mention, even in passing, of applying the standard for overexpression recited in claim 13 to the invention as originally described, which includes adenovirus where ADP expression is increased by means other than removing splice sites and E3 coding sequences as in the KD and GZ vectors, see page 13, lines 2-8. At best, the claim limitation applies only to embodiments involving the KD and GZ vectors.

Claim 32 recites that ADP overexpression "is detectable by western blot, cell lysis, virus release, or by cell spreading assay." Claims 103-106 recite these individually. Applicant indicates that Fig. 2 and Example 2 support this limitation with respect to cell lysis or cell spreading assay. However, Example 2 does not teach that any of these methods are to be used to determine whether ADP is overexpressed. Instead, these assays were used to characterize KD1 and KD3 infection, and the consequence of ADP overexpression. Example 2 discloses that overexpression of ADP in the case of KD1 and KD3 leads to an increased rate of cell lysis, more rapid virus release, and increased cell spreading as compared to dl309, *dl*01/07, and Ad5. It does not suggest that either assay is to be used to determine whether ADP is overexpressed by a given adenovirus vector used in the invention. While ADP overexpression may lead to increased rate of cell lysis, virus release or cell spread, it does not follow that an increased rate of cell lysis or cell spread displayed by an adenovirus vector, whose level of ADP expression is unknown, means the adenovirus vector overexpresses ADP, as is implied by the claim limitations.

Taking characteristics of an individual embodiment and making that characteristic the basis of a generic claim without further supporting disclosure is not in compliance with the written description requirement. See *Purdue Pharma L.P. v. Faulding Inc.*, 56 USPQ2d 1481, 1487 (CAFC 2000). Consequently, there is no evidence that Applicant contemplated the instantly claimed genus at the time the original specification was filed.

With respect to claim 60, and its dependent claims, claim 60 recites a series of four structural features (a)-(d) characterizing the "adenovirus vector." In particular it recites "a) …; b) …; c) …, and/or d) …". The inclusion of "and/or" indicates that at least one of these characteristics is present or all four of the characteristics are present. Applicant indicates that

these limitations are supported by the specification at page 12, lines 33-35 and page 13, lines 2-8. However, the original specification presents these four characteristics as alternatives for achieving ADP overexpression. It does not teach or even imply including more than one of these alternatives within a single adenovirus vector, as would be the case where a), b), c), and d) were included. This part of the rejection would be overcome by replacing ", and/or" with --; or --. (The comma should be a semi-colon in any event).

Applicant's arguments filed 12/8/03 have been fully considered but they are not persuasive. Applicant argues that Example 1 when viewed with the general discussion would show that "previously known viruses such as *dl*309 were intended to be a general "measuring stick" for overexpression". In response, the specification does not teach that any one adenovirus is the yardstick, even in the case of the KD and GZ vectors, comparison was made to several adenoviruses that were close in structure to the KD and GZ vectors. In the general discussion, the specification indicates that the measure would be ADP molecules per viral genome against all previously known adenoviruses (page 12. lines 18-21), not against any one adenovirus chosen in hindsight after the application was filed. Also, the specification does not disclose that the KD and GZ vectors were compared to any adenovirus in terms of directly measured ADP molecules per viral genome. In addition, while the specification shows that early after infection, ADP is expressed in higher amount than *dl*309, for example, late in infection ADP levels in KD, GZ, and *dl*309 infected cells were comparable. In order for ADP levels in *dl*309 to have risen to comparable levels at the later timepoint, ADP expression in *dl*309 must have exceeded that of the KD and GZ vectors at later during infection.

With respect to the limitations of claims 32 and 103-106, Applicant is missing the point. The different assays mentioned in these claims were used to characterize the effect of ADP expression in the KD and GZ infected cells relative to other adenoviruses, not to determine whether a given adenovirus overexpressed ADP. Applicant has failed to indicate where the specification teaches that these methods are to be used to determine whether a given adenovirus meets the limitations of the claims or not.

With respect to claim 60, the connector "and" used on page 13, lines 2-8, does not imply that the alternatives are to be combined. Page 12, line 32, to page 13, line 8 describes some of the "multitude of ways" that ADP overexpression may be accomplished. Page 13, lines 2-8, lists "other means" than deleting splice sites from the E3 region, as in the KD and GZ, vectors. This paragraph never suggests that these "ways" or "means" should be combined, much less that all of them should be combined, as recited in claim 60.

Claims 101-102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 101 and 102 each recite the phrase "overexpresses an adenoviral death protein," which renders these claims unclear as to the metes and bounds of the adenoviral vector. It is unclear in what context "overexpresses" is directed or applied to (i.e. overexpresses relative to what?). Wild-type adenoviruses typically "overexpress" ADP at very late stages of the infection cycle. Thus, a reasonably broad interpretation of these claims would suggest any adenovirus

carrying ADP operably linked to its native promoters, and subject to natural expression control would inherently meet the limitation of the claims as written.

Claim Rejections - 35 USC § 102 & 103

Claims 10-13, 32-44, 60, 61, 68, 69, 72-75, and 97-99 remain rejected and claims 101-108 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by either Henderson et al. (U.S. 6,197,293, filed 3/02/98), or Little et al. (U.S. 6,254,862, filed 3/02/98) for the reasons of record set forth in the Office action of 9/3/03.

Claims 13, 20-22, 60, and 64-66 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al. (U.S. 6,197,293, filed 3/02/98), or Little et al. (U.S. 6,254,862, filed 3/02/98) as applied to claims 10-13, 32-44, 60, 61, 68, 69, 72-75, 97-99, and 101-108 above, and further in view of Freytag (Hum. Gene Ther. 9: 1323-1333, 1998) for the reasons of record set forth in the Office action of 9/3/03.

Applicant's arguments filed 12/8/03 have been fully considered but they are not persuasive. First Applicant argues that Henderson and Little do not teach an adenoviral vector that "overexpresses" ADP. While it is true that neither reference characterizes any adenoviral vector as overexpressing ADP, the issue is whether the ADP expressing vectors they disclose would meet the limitations of the instant claims. See MPEP 2112.01. When the PTO has sound reason to believe that the prior art teaches a product that meets the limitations of a claim, Applicant bears the burden to prove that the prior art product does not. The PTO does not have a

laboratory in which to compare the properties of the claimed adenovirus to that of the prior art adenovirus.

The instant specification has been relied upon for its teachings of the structural features of adenoviral vectors (i.e. the means) that would result in overexpression of ADP. The instant specification teaches that one way to achieve overexpression of ADP is to remove "a splice site for any of the E3 mRNAs." CN751 is very close in structure to the instant GZ3 vector, which has a wild type E1 region, and the E3 region of CN751 is very close to that of instant KD1 (see Office action of 3/18/03 at pages 12-13 for analysis). All of the coding regions and apparently all of the splice sites of the E3 region are missing in CN751. With respect to the teachings in the references to place ADP under control of a heterologous promoter, the instant specification teaches that this is another "means" for overexpressing ADP (page 13). When adenoviral control of expression of ADP is removed, it is not responsive to regulation that would normally suppress expression of ADP, such as occurs early in infection. Consequently, placing ADP expression under control of a heterologous promoter would be expected to increase its expression relative to wild type adenovirus, at least at early stages of infection. With respect to the teaching in Little to include multiple copies of the ADP gene, this would be expected to increase ADP expression due to the increased copy number of the ADP coding sequence, i.e. a gene dosage effect.

In Applicant's response filed 1/10/02, Applicant had stated "Both of theses references disclose a recombinant adenoviral vector which is replication-restricted to neoplastic cells and which overexpresses an adenoviral death protein," in reference to CN751. Applicant asserts, without supporting evidence, that this statement was a recitation of the pending rejection, which failed to attribute the statement to the examiner. However, this statement is followed by

arguments that the Applicant's conception of the claimed invention antedated the priority dates of the two patents. No arguments were presented that the patents did not teach embodiments embraced by the claims. When the statement is taken as written and in the context of the arguments as a whole, the statement clearly appears to be an acceptance by Applicant that CN751 would overexpress ADP. Thus, the Office has sound reasons to believe that adenoviruses disclosed in the references would meet the limitations of claims requiring overexpression of ADP.

Second, Applicant argues that the claimed invention was conceived before the priority dates of the prior art patents, and that Applicant showed due diligence to reducing the conception to practice. The declaration filed on 12/8/03 under 37 CFR 1.131 has been considered but is ineffective to overcome the Henderson or Little references. The evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Henderson or Little references. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). Para. 3 of the declaration refers to Exh. B of the 1/6/03 declaration as demonstrating conception of the claimed subject matter. However, this exhibit does not show evidence of conception of the instantly claimed subject matter, i.e. a method of treating cancer with an adenoviral vector that is replication-competent in neoplastic cells and overexpresses ADP. Exhibit B is a research proposal to identify vectors that would promote cell death, and to determine whether ADP expression (including from non-adenoviral vectors) was sufficient to

promote cell killing. As indicated on page 5 of the exhibit referring to adenoviral vectors, "the vector should probably be defective." Thus, the exhibit teaches away from using adenoviral vectors that are "replication-competent in neoplastic cells." There is no evidence in Exhibit B that Applicant had conceived of the KD or GZ vectors, specifically, or generic adenoviral vectors that are replication-competent in neoplastic cells and that "overexpress" ADP. Thus, there is no nexus between this exhibit and the remainder of the exhibits provided in this declaration or the declaration of 1/6/03.

With respect to the broader teachings in the patents, the instant claims are generic to any adenoviral vector that overexpresses ADP, not just adenoviral vectors of the KD or GZ type, where deletions have been made in E3. The patents disclose this type of adenoviral vectors and other types that would be expected to "overexpress" ADP, e.g. multiple copies of ADP gene, ADP gene under control of a viral or tissue specific heterologous promoter. The 12/8/03 declaration does not demonstrate conception of the claimed invention as a whole, where any means to overexpress ADP is embraced. The patents describe more types of adenovirus that would be expected to read on the instant claims.

With respect to the reduction of practice of KD1 before the priority dates of the patents, while KD1 had been constructed, the declaration shows that it was not known before the priority date that it overexpressed ADP. If it was not known until after the priority dates that KD1 overexpressed ADP, how then could Applicant have conceived of its suitability in the instantly claimed invention before the priority dates.

With respect to *In re Hostettler* showing that to demonstrate priority, prior possession of only one embodiment within the scope of the claim need be shown. This is not a hard and fast

rule, particularly where the art is unpredictable, see MPEP 715.03. Applicant has not demonstrated possession of as much of the claimed generic invention as is shown in the patents. Furthermore, Applicant has yet to demonstrate prior conception of using even KD1 in the method being claimed, or that KD1 would overexpress ADP.

In response to applicant's arguments against the Freytag reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The connection between Henderson or Little and Freytag was explained in the rejection. That Freytag fails to mention ADP is irrelevant, since such teachings were provided in the primary references. With respect to claims 13 and 60, these claims are cited in the rejection because the other rejected claims depend from them, and claims 13 and 60 explicitly embrace the subject matter that is the focus of the rejection by virtue of the dependent claims.

Double Patenting

Claims 10-13, 32-44, 60, 61, 72-75, and 97-108 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,627,190. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims embrace the embodiment represented in the claims of the '335 application, wherein the adenovirus vector is replication restricted to cells expressing a telomerase in light of the supporting disclosure in the specification.

This rejection had previously been made as a provisional rejection over Application No. 09/956,335. This application has since issued as a patent, and the rejection is no longer provisional.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy J. Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe
Primary Examiner
Art Unit 1632